Finding of No Significant Impact (FONSI)

Removal of Essential–Use Designation

Albuterol Used in Oral Pressurized Metered Dose Inhalers (MDIs)

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FINDING OF NO SIGNIFICANT IMPACT

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. Under the Clean Air Act (CAA), the Food and Drug Administration (FDA), in consultation with the Environmental Protection Agency (EPA), is required to determine whether an FDA-regulated product that contains an ozone depleting substance (ODS), such as chlorofluorocarbons (CFCs), is essential. Furthermore, Section 612 of the CAA requires EPA to establish a program to identify alternatives to Class I and II ODSs and to publish a list of acceptable and unacceptable substitutes (Significant New Alternatives Policy (SNAP)). The regulations at 21 CFR 2.125, *Use of Ozone-Depleting Substances; Essential-Use Determinations*, provides standards that FDA uses to determine which FDA-regulated products that contain an ODS are essential under the CAA. The attached environmental assessment (EA) constitutes the agency's environmental review for removal of the essential-use designation for albuterol MDIs under 21 CFR 2.125(g)(4). If the essential-use designation is removed, albuterol MDIs containing an ODS could not be marketed in the U.S. after a suitable transition period.

From an environmental perspective, removal of the essential-use designation for albuterol MDIs is clearly preferred. This action would eliminate the use of CFC propellants in albuterol MDI products while providing a continued supply of the drug product that uses a propellant (HFA-134a) that has been determined by EPA under its SNAP program to be an acceptable substitute for certain ODSs, including CFC-11. HFA-134a has zero ozone depletion potential but is a greenhouse gas. Removal of the essential-use designation for albuterol MDIs is consistent with the U.S. policy of limiting the production and use of ozone depleting substances (ODSs), including chlorofluorocarbons (CFCs), and would benefit the environment by reducing the use of ozone depleting CFC propellants.

The FDA, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of removing the essential-use designation for the identified product and has concluded that this action will not, individually or cumulatively, have a significant adverse effect on the quality of the human environment and therefore an environmental impact statement is not required.

May 6, 2004 Florian Zielinski
DATE PREPARED BY
Florian Zielinski
Chemist
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

Environmental Assessment

Removal of Essential–Use Designation

Albuterol Used in Oral Pressurized Metered Dose Inhalers (MDIs)

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

Environmental Assessment

Date

December 15, 2003

2. Agency Preparing the Environmental Assessment (EA)

Center for Drug Evaluation and Research
Food and Drug Administration

3. Address

5600 Fishers Lane
Rockville, MD 20857

4. Description of the Proposed Action

The Food and Drug Administration (FDA) is proposing to amend its regulation on the use of ozone depleting substances (21 CFR 2.125) to remove the essential-use designation for albuterol used in oral pressurized metered dose inhalers (MDIs).

This EA evaluates the potential environmental impacts of removing the essential-use designation for these products.

5. Identification of Substance that are the Subject of the Proposed Action

Essential-use designation will be removed for albuterol MDI products:

Drug Substance: Albuterol

Chemical Names:

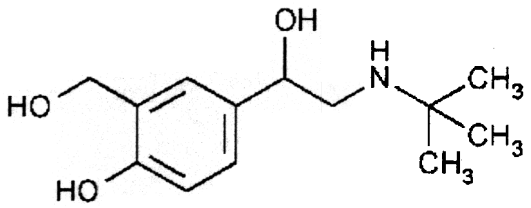
1,3-Benzenedimethanol, α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-.
α^1-[(*tert*-Butylamino)methyl]-4-hydroxy- *m*-xylene-α,α'-diol

CAS #: 18559-94-9

Molecular Weight: 239.31

Molecular Formula: $C_{13}H_{21}NO_3$

Structural Formula:



6. Environmental Issues

A. Background

The link between CFCs and the depletion of stratospheric ozone was established in the mid-1970's and since 1978 the U.S. government has pursued a consistent policy of limiting the production and use of ozone depleting substances (ODSs),[1] including chlorofluorocarbons (CFCs).

In 1978, FDA finalized a programmatic environmental impact statement (EIS) regarding the use of CFCs in products subject to regulation by the agency under the Federal Food, Drug, and Cosmetic Act. This EIS was used as the basis for prohibiting use of CFCs as propellants in self-pressurized containers if the use of the CFC was not deemed to be essential. As stated in the EIS:

> The Commissioner of Food and Drugs has concluded that the continued use of chlorofluorcarbon propellants in self-pressurized containers in products subject to the Federal Food, Drug, and Cosmetic Act (FFD&C) poses an unreasonable risk of long-term biological and climatic impacts.
>
> Accordingly, the Food and Drug Administration is finalizing a prohibition of the nonessential-use of chlorofluorocarbons as propellants in self-pressurized (aerosolized) containers in products subject to the FFD&C Act. The products to which the regulation applies are human food, food additives, human drugs, including biological products, animal food, animal drugs, cosmetics, and medical devices. (p. iii).

On September 16, 1987, the United States committed to reducing production and importation of certain CFCs by signing, with 22 other countries, the Montreal Protocol on Substances that Deplete the Ozone Layer. The 1990 amendments to the Clean Air Act (CAA), were designed in part to phase out the use of ODSs in the United States. Under the CAA, FDA, in consultation with the Environmental Protection Agency (EPA), is required to determine whether an FDA-regulated product that contains an ODS, such as

[1] Any class I substance as defined in 40 CFR part 82, appendix A to subpart A or class II substance as defined in 40 CFR part 82, appendix B to subpart A.

CFC, is essential. Furthermore, Section 612 of the CAA requires EPA to establish a program to identify alternatives to Class I and II ODSs and to publish a list of acceptable and unacceptable substitutes (Significant New Alternatives Policy (SNAP)).

FDA's regulations at 21 CFR 2.125, *Use of Ozone-Depleting Substances; Essential-Use Determinations*, provides standards that FDA uses to determine which FDA-regulated products that contain an ODS are essential under the CAA. This EA constitutes the agency's environmental review for removal of the essential-use designation for albuterol MDIs under 21 CFR 2.125(g)(4). If the essential-use designation is removed, albuterol MDIs containing an ODS could not be marketed in the U.S. after a suitable transition period.

B. Environmental Effects of ODS and non-ODS Propellants

Albuterol MDIs were first approved for use in the United States in 1981 for the treatment of broncospasms associated with asthma and chronic obstructive pulmonary disease (COPD). Albuterol MDIs have historically used trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) as propellants. Currently there are multiple applications approved for albuterol MDIs that use CFC-11 and/or CFC-12 as the propellant. As described in the background section 6.A above, CFCs have been linked to the depletion of stratospheric ozone. Once in the stratosphere, CFCs are broken down by ultraviolet light, creating chlorine free radicals that then deplete stratospheric ozone.

FDA has approved two albuterol sulfate MDIs that use hydrofluroalkane, HFA-134a[2], as the propellant rather than CFCs:

- NDA 20-503, Proventil HFA (August 15, 1996)[3]
  NDA 20-983, Ventolin HFA (April 19, 2001)

EPA has evaluated HFA-134a under its SNAP program and has determined that it is an acceptable substitute for certain ODSs used as aerosol propellants including CFC-11. HFA-134a is nonflammable and has been characterized as having low toxicity and zero ozone depletion potential. HFA-134a is a greenhouse gas.

Mitigation Measures

The U.S. government has pursued a consistent policy of limiting the production and use of ODSs, including CFCs. Under EPA's SNAP program no conditions or restrictions are specified for HFA-134a.

8. Alternatives Including the Proposed Action

[2] HFA-134a is referred to as HFC-134a under EPA's SNAP program

[3] An environmental assessment and FONSI were prepared for this application.

A. Alternative 1: No Action

The no action alternative is to retain the current essential-use designation for albuterol. This would permit the continued marketing of albuterol MDIs that use CFCs as the propellant.

B. Alternative 2: Removal of the Essential-use Designation for Albuterol MDIs

With this alternative, albuterol MDIs containing an ODS could not be marketed in the U.S. after a suitable transition period. The only albuterol MDIs that could be marketed after the transition period would be those that do not contain an ODS.

C. Evaluation of Alternatives

As described in section 6 above, CFCs have been linked to the depletion of stratospheric ozone. Once in the stratosphere, CFCs are broken down by ultraviolet light, creating chlorine free radicals that then deplete stratospheric ozone. Alternative 1 would allow the continued use of albuterol MDIs that use ODSs, including CFCs, as propellants.

Under alternative 2, the proposed action, albuterol MDIs containing an ODS could not be marketed in the U.S. after a suitable transition period. The only albuterol MDIs that could be marketed after the transition period would be those that do not contain an ODS. Currently there are two albuterol MDIs approved by FDA that do not use an ODS. These products use the propellant HFA-134a. EPA has evaluated HFA-134a under its SNAP program and has determined that it is an acceptable substitute for certain ODSs used as aerosol propellants, including CFC-11. HFA-134a has zero ozone depletion potential but is a greenhouse gas.

D. Conclusion

From the environmental perspective, alternative 2 is clearly preferred. It would eliminate the use of CFCs in albuterol MDI products while providing a continued supply of the drug product that uses a propellant (HFA-134a) that (1) has been found acceptable by EPA under its SNAP program and (2) has no ozone depletion potential. Choosing alternative 2 is consistent with the U.S. policy of limiting the production and use of ODSs, including CFCs and would benefit the environment by reducing the use of ozone depleting CFC propellants.

9. List of Preparers

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10. References

EPA's Significant New Alternatives Policy (SNAP)
http://www.epa.gov/spdpublc/snap/index.html>

EPA's regulations implementing the Montreal Protocol; 40 CFR Part 82

FDA's Environmental Assessment and FONSI for NDA 20-503 (available in this docket)

FDA's Final Environmental Impact Statement; *Fluorocarbons: Environmental and Health Implications* (available in this docket)

FDA's regulations on *Use of Ozone-Depleting Substances; Essential-Use Determinations;* 21 CFR 2.125

Montreal Protocol on Substances that Deplete the Ozone Layer; S. Treaty Doc. No. 10, 100th Cong., 1st sess., 26 I.L.M. 1541 (1987)

11. Appendices

None